NCI GUIDELINES: EXPEDITED ADVERSE EVENT REPORTING REQUIREMENTS FOR NCI INVESTIGATIONAL AGENTS

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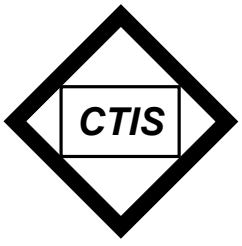

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SECTION 1: ADVERSE EVENT TERMINOLOGY AND DEFINITIONS

1.1 **ADVERSE EVENT** – Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite).

1.2 **LIFE-THREATENING ADVERSE EVENT** – Any adverse event that places the patient or subject, in view of the investigator, at immediate risk of death from the reaction.

1.3 **SERIOUS ADVERSE EVENT (SAE)** – Any adverse event occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

Please note for **hospitalization** – All hospitalizations (or prolongation of existing hospitalization) for medical events equivalent to CTC Grade 3, 4, 5 must be reported regardless of the requirements for Phase of study, expected or unexpected and attribution. For example, do not report an admission for pharmacokinetic sampling, but do report an admission for a myocardial infarction.

1.4 **TOXICITY** – Toxicity is a term NOT clearly defined by regulatory organizations. Toxicity has been described as an adverse event that has an attribution of possibly, probably or definitely related to investigational treatment. To minimize confusion the NCI would recommend that the term toxicity NOT be utilized for adverse event reporting purposes.

The CTC continues to use the term 'toxicity' because of familiarity.

1.5 **UNEXPECTED ADVERSE EVENT** – Any adverse event which is not listed in the NCI Agent Specific Expected Adverse Event List. This list is updated electronically in real time.

1.6 **ADVERSE EVENT EXPEDITED REPORTING SYSTEM (AdEERS)** (formerly known as Adverse Drug Reaction Reporting) – An electronic system for expedited submission of adverse event reports.

1.7 **ATTRIBUTION** – The determination of whether an adverse event is related to a medical treatment or procedure. Attribution categories:

Definite - The adverse event *is clearly related* to the investigational agent(s).

Probable - The adverse event *is likely related* to the investigational agent(s).

Possible - The adverse event *may be related* to the investigational agent(s).

Unlikely - The adverse event *is doubtfully related* to the investigational agent(s).

Unrelated - The adverse event *is clearly NOT related* to the investigational agent(s).

1.8 **COMMON TOXICITY CRITERIA (CTC)**[1] – The CTC provides a descriptive terminology which is to be utilized for adverse event reporting. A grading (severity) scale is provided for each adverse event term.

[1] All studies reviewed and approved after March 5, 1998 must utilize the CTC version 2.0 standards 1998 for adverse event grading and attribution.

1.9 **GRADE** – Severity of the adverse event. Grades were developed using the following general guidelines:

0 - No adverse event or within normal limits

1 - Mild adverse event

2 - Moderate adverse event

3 - Severe adverse event

4 - Life-threatening or disabling adverse event

5 - Fatal adverse event

1.10 **INVESTIGATIONAL AGENT**[2] – An agent sponsored under an Investigational New Drug Application (IND).

Note: An FDA approved agent may on occasion be used under an IND for an unapproved indication, dose, schedule or route of administration. Please refer to the protocol document to determine if an agent is investigational or commercial and follow the guidelines within the protocol for adverse event reporting.

1.11 **COMMERCIAL AGENT** – Any agent not supplied under an IND but obtained instead from a commercial source.

1.12 **FINAL STUDY REPORT** – Summary reporting at study completion. The minimal data requirements for a final study report are summaries of accrual, demographics, adverse events, deaths on study, and study results.

1.13 **CLINICAL DATA UPDATE SYSTEM (CDUS)** – The CDUS is the primary resource of clinical data for the NCI Division of Cancer Treatment and Diagnosis (DCTD).

1.14 **CLINICAL TRIALS MONITORING SERVICE (CTMS)** – The CTMS is the non-Governmental organization contracted by CTEP to receive, review and perform data management tasks on individual patient case report forms for Phase 1 investigational agent studies designated for CTMS data reporting.

1.15 **ROUTINE STUDY REPORTING** – Scheduled reporting (rather than expedited reporting) throughout a study (e.g., CDUS or CTMS). Routine study reports include adverse event information for each patient by course for all Phase 1 and 2 studies that utilize a DCTD-sponsored and supplied investigational agent.

[2] The NCI Guidelines for Expedited Adverse Event Reporting apply only to investigational agents supplied under an IND sponsored by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

SECTION 2: EXPEDITED ADVERSE EVENT REPORTING REQUIREMENTS FOR INVESTIGATIONAL AGENTS SPONSORED BY NCI

2.1 GUIDELINES FOR ADVERSE EVENT REPORTING

Adverse event collection and reporting is a routine part of every clinical trial. The first step is to identify the event using the Common Toxicity Criteria (CTC). The severity of the event should then be graded using the CTC criteria. Next, determine if the adverse event is related to the medical treatment or procedure (attribution). If so, determine whether the adverse event is expected or unexpected. With this information and the adverse event reporting section in each protocol, the investigator can determine whether an adverse event should be reported to the NCI as an expedited report (AdEERS) or a routine report (CDUS or CTMS) (see Attachment C paradigm).

2.1.1 Persistent/Recurring Adverse Events – An adverse event that persists/recurs from one course (cycle) to another should only be reported in an expedited manner once unless the grade becomes more severe in a subsequent course. An adverse event, which **resolves and then recurs** during a different course (cycle) is only reported in a routine manner unless the severity changes.

- A patient experiences Grade 3 thrombocytopenia during cycle one. During cycle two the adverse event persists/recurs but the severity remains unchanged. During cycle three the adverse event persists/recurs but increases in severity to Grade 4. The following should be submitted as expedited reports (if thrombocytopenia is not already on the NCI Agent Specific Expected Adverse Event List):

  Cycle One – Grade 3 Thrombocytopenia (Expedited Report via AdEERS and Routine Reporting via CDUS or CTMS)

  Cycle Two – Persistence/Recurrence of Grade 3 Thrombocytopenia (No Expedited Report but Routine Reporting via CDUS or CTMS)

  Cycle Three – Grade 4 Thrombocytopenia (Expedited Report via AdEERS and Routine Reporting via CDUS or CTMS)

2.1.2 Baseline Adverse Events – An expedited adverse event report should NOT be submitted if a patient is entered on a study with a preexisting condition (e.g., elevated laboratory value). If the preexisting condition worsens in severity, the investigator should re-assess the event to determine if an adverse event should be reported (determine attribution). If the adverse event resolves and then recurs, the investigator should re-assess the event to determine if the event should be reported. No modification in grading should be made to account for abnormalities existing at baseline. For example:

- A patient enters a trial with an AST equivalent to Grade 1. If the AST remains unchanged while on protocol, an expedited adverse event report should NOT be submitted. If at any time while on protocol, the AST is Grade 2, an expedited adverse event report is required if the event is unexpected and the attribution is at least possible. An expedited report is NOT required if the AST is expected regardless of attribution. If at any time while on protocol, the AST is Grade 3, an expedited adverse event report would be required if the AST is either expected or unexpected and resulted in hospitalization (or prolongation of existing hospitalization) regardless of attribution or if the AST is unexpected and the attribution is at least possible. An expedited adverse event report is NOT required if the AST is expected and did not require hospitalization (or prolongation of existing hospitalization) regardless of attribution or if the AST is unexpected, but did not require hospitalization (or prolongation of existing hospitalization) and had an attribution of unrelated or unlikely. Routine reporting would be required as specified by CDUS or CTMS.
- A patient enters a study with diarrhea equivalent to Grade 2. The diarrhea resolves during the first cycle of therapy. If, during a subsequent cycle the patient experienced Grade 2 diarrhea, the adverse event should be re-assessed and reported if it fulfills expedited adverse event reporting guidelines.

2.1.3 Investigational Agent(s) used in a Clinical Trial Involving a Commercial Agent(s) on Separate Arms – An expedited adverse event report should be submitted for an investigational agent(s) (supplied under an NCI-sponsored IND) used in a clinical trial involving a commercial agent(s) on a separate arm only if the event is specifically associated with the investigational agent(s). Routine reporting of adverse events via CDUS or CTMS is used for all arms of a study including commercial agents.

2.1.4 Investigational Agent(s) used in a Clinical Trial in Combination with a Commercial Agent(s) – When an investigational agent(s) (supplied under an NCI-sponsored IND) is used in combination with a commercial agent(s), the combination should be considered investigational. Expedited reporting of adverse events should follow the guidelines for investigational agents as specified on page 5 of these guidelines.

SECTION 3: EXPEDITED ADVERSE EVENT REPORTING REQUIREMENTS

3.1 Reporting requirements and timing of reporting are dependent on the Phase of trial, grade, attribution and whether the event is expected or unexpected as determined by the NCI Agent Specific Expected Adverse Event List, protocol and/or Investigator's Brochure. An expedited adverse event report requires submission to CTEP via AdEERS or the *Adverse Event Expedited Report – Single Agent* or *Multiple Agents* paper templates (available on the CTEP Home Page, http://ctep.info.nih.gov). Reports should be submitted within the timeframes specified below. All expedited adverse event reports should also be sent to the local Institutional Review Board (IRB). Routine adverse events are normally reported in the annual report to the IRB.

3.2 Attribution – An expedited report is required for all unexpected and expected Grade 4 and Grade 5 adverse events regardless of attribution for any Phase of trial (1, 2, 3). An expedited report is required for unexpected Grade 2 and Grade 3 adverse events with an attribution of possible, probable or definite for any Phase of trial (1, 2, 3). An expedited report is not required for unexpected or expected Grade 1 adverse events for any Phase of trial (1, 2, 3).

3.3 Expedited reports on the *Adverse Event Expedited Report – Single Agent* or *Multiple Agents* paper templates are to be sent to - Investigational Drug Branch (IDB), PO Box 30012, Bethesda, MD 20824 or by fax to (301) 230-0159.

3.4 Telephone reports to IDB (301) 230-2330 available 24 hours a day (recorder after hours 5pm to 9am EST).

3.5 After September 30, 2000, all expedited reports must be submitted using the new AdEERS web application or the *Adverse Event Expedited Report - Single Agent or Multiple Agents* paper templates. The AdEERS standard is implemented for all trials regardless of dates of review and approval. Expedited reports submitted using any of the previous adverse event forms will not be acceptable. Assistance for using AdEERS or for completion of the AdEERS templates is available at http://ctep.info.nih.gov.

3.6 Expedited reporting may not be appropriate for certain protocols where an adverse event is expected. The exception or acceptable reporting procedures must be specified in the text of the approved protocol. Therefore, the protocol guidelines would supersede the standard guidelines (Tables A and B) for adverse event reporting.

TABLE A: Expedited Reporting for Phase 1 Studies

UNEXPECTED EVENT		EXPECTED EVENT	
GRADES 2 – 3 Attribution of Possible, Probable or Definite	**GRADES 4 and 5 Regardless of Attribution**	**GRADES 1 – 3**	**GRADES 4 and 5 Regardless of Attribution**
Grade 2 – Expedited report within 10 working days. **Grade 3** – Report by phone to IDB within 24 hrs. Expedited report to follow within 10 working days. (**Grade 1** – Adverse Event Expedited Reporting NOT required.)	Report by phone to IDB within 24 hrs. Expedited report to follow within 10 working days. This includes deaths within 30 days of the last dose of treatment with an investigational agent.	Adverse Event Expedited Reporting NOT required.	Report by phone to IDB within 24 hrs. Expedited report to follow within 10 working days. This includes deaths within 30 days of the last dose of treatment with an investigational agent

TABLE B: Expedited Reporting for Phase 2 and Phase 3 Studies

UNEXPECTED EVENT		EXPECTED EVENT	
GRADES 2 – 3 Attribution of Possible, Probable or Definite	**GRADES 4 and 5 Regardless of Attribution**	**GRADES 1 – 3**	**GRADES 4 and 5 Regardless of Attribution**
Expedited report within 10 working days. (Grade 1 Adverse Event Expedited Reporting NOT required.)	Report by phone to IDB within 24 hrs. Expedited report to follow within 10 working days.	Adverse Event Expedited Reporting NOT required.	Expedited report, including Grade 5 Aplasia in leukemia patients, within 10 working days. Grade 4 Myelosuppression not to be reported, but should be submitted as part of study results. Other Grade 4 events that do not require expedited reporting would be specified in the protocol.

TABLE C1: Summary of Expedited Reporting for Investigational Agents for Phase 1, Phase 2, and Phase 3

ATTRIBUTION	ADVERSE EVENT									
	GRADE 1		GRADE 2		GRADE 3 and/or *Hospitalization		GRADE 4 and/or *Hospitalization		GRADE 5 and/or *Hospitalization	
	UNEXPECTED	EXPECTED	UNEXPECTED	EXPECTED	UNEXPECTED	EXPECTED	UNEXPECTED	EXPECTED	UNEXPECTED	EXPECTED
UNRELATED					*	*	AdEERS	AdEERS	AdEERS	AdEERS
UNLIKELY					*	*	AdEERS	AdEERS	AdEERS	AdEERS
POSSIBLE			AdEERS		AdEERS	*	AdEERS	AdEERS	AdEERS	AdEERS
PROBABLE			AdEERS		AdEERS	*	AdEERS	AdEERS	AdEERS	AdEERS
DEFINITE			AdEERS		AdEERS	*	AdEERS	AdEERS	AdEERS	AdEERS

AdEERS – ADVERSE EVENT EXPEDITED REPORTING SYSTEM

*** For Hospitalization Only – Any medical event equivalent to CTC Grade 3, 4, 5 which precipitated hospitalization (or prolongation of existing hospitalization) must be reported regardless of requirements for Phase of study, expected or unexpected and attribution.**

Expedited reporting may not be appropriate for certain protocols where an adverse event is expected. In those situations the exception or acceptable reporting procedures must be specified in the text of the approved protocol. For example, a Grade 4 event definitely-related and planned by trial design (e.g., in a trial of an agent designed to produce Grade 4 diarrhea) is only to be reported if the patient is hospitalized.

TABLE C2: Routine Adverse Event Reporting Requirements for Complete CDUS or CTMS

ATTRIBUTION	ADVERSE EVENT				
	GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**	**GRADE 5**
UNRELATED	CTMS	CTMS	CTMS	CTMS CDUS	CTMS CDUS
UNLIKELY	CTMS	CTMS	CTMS	CTMS CDUS	CTMS CDUS
POSSIBLE	CTMS CDUS	CTMS CDUS	CTMS CDUS	CTMS CDUS	CTMS CDUS
PROBABLE	CTMS CDUS	CTMS CDUS	CTMS CDUS	CTMS CDUS	CTMS CDUS
DEFINITE	CTMS CDUS	CTMS CDUS	CTMS CDUS	CTMS CDUS	CTMS CDUS

CDUS – COMPLETE CLINICAL DATA UPDATE SYSTEM

CTMS – CLINICAL TRIALS MONITORING SERVICE

Report using the method (CDUS or CTMS) as specified in the protocol. (See Attachment A, page 8)

Attachment A: ROUTINE ADVERSE EVENT PROTOCOL REPORTING THROUGH THE CLINICAL DATA UPDATE SYSTEM (CDUS) OR THE CLINICAL TRIALS MONITORING SERVICE (CTMS)

Routine adverse event reporting requirements for CDUS or CTMS are dependent on the Phase of trial, grade, and attribution. The method of reporting is identified in the protocol approval letter. All studies reviewed and approved after March 5, 1998 utilize the CTC version 2.0 standards for adverse event naming, grading and attribution.

A.1 CTMS

A.1.1 Trial Types – For early Phase 1 trials (initial studies of an investigational agent or combination of investigational agents in a patient population) that utilize a DCTD sponsored and supplied investigational agent.

A.1.2 Report Grade 1 to 5 regardless of attribution.

A.1.3 Frequency – Biweekly (every 14 days).

A.2 CDUS (Complete)

A.2.1 Trial Types – For late Phase 1 and Phase 2 trials that utilize a DCTD sponsored and supplied investigational agent.

A.2.2 Report all Grade 1 to 3 adverse events with an attribution of *possible, probable, definite.* All Grade 4 and 5 adverse events, regardless of attribution, must be reported.

A.2.3 Frequency – Quarterly (Jan. 31, Apr. 30, July 31, and Oct. 31).

A.3 CDUS (Abbreviated)

Note: Routine adverse event reporting is NOT required for those trials assigned to abbreviated CDUS.

A.3.1 Trial Types.

A.3.1.1 Phase 3.

A.3.1.2 Phase 1 and 2 that do NOT utilize a DCTD sponsored and supplied investigational agent.

A.3.1.3 Division of Cancer Prevention (DCP) studies.

A.3.2 Grade/Attribution requirements – None.

A.3.3 Frequency – Not applicable.

A summary of the reporting requirements for CDUS or CTMS is provided in Table C2 (page 7). All adverse events must be reported by the course (cycle) they occurred. Only the highest-grade of each adverse event type should be reported during a given course. An attribution must be assigned to all reported adverse events.

Note: The CDUS or CTMS is not a substitute for submission of expedited reports. All adverse events that require expedited reporting should be reported as outlined in Section 3 of these Guidelines.

Attachment B: ADVERSE EVENT REPORTING FOR COMMERCIAL AGENTS

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. In some cases an agent obtained commercially may be used for indications not included in the package label. In addition, NCI may on some occasions distribute commercial supplies for a trial. Even in these cases, the agent is still considered to be a commercial agent and, unless specified otherwise in the protocol, the following procedures should be followed:

Refer to the pharmaceutical section of the protocol document to determine if an agent is investigational or commercial. Also see Sections 1.10 and 1.11 of these Guidelines for definitions.

B.1 **WHAT TO REPORT:** An unexpected (not listed in the package label), life-threatening (Grade 4) or unexpected, fatal (Grade 5) adverse event with an attribution of possible, probable or definite.

B.2 **WHEN TO REPORT:** These events should be reported within ten (10) working days.

B.3 **WHERE TO REPORT:** These adverse events with commercial agents must be reported to the FDA and a copy provided to the NCI using the MedWatch form. A copy of the MedWatch form can be obtained from the FDA's MedWatch Web site (see below) or the CTEP home page in Appendix 12 of the Investigator's Handbook. The MedWatch report can be sent by the following mechanisms:

B.3.1 To the FDA:

B.3.1.1 MedWatch online at the MedWatch Web site - www.fda.gov/medwatch

B.3.1.2 By mail: MedWatch
5600 Fishers Lane
Rockville, Maryland 20852-9787

B.3.1.3 By fax at 1-800-332-0178

B.3.2 Copy to the NCI:

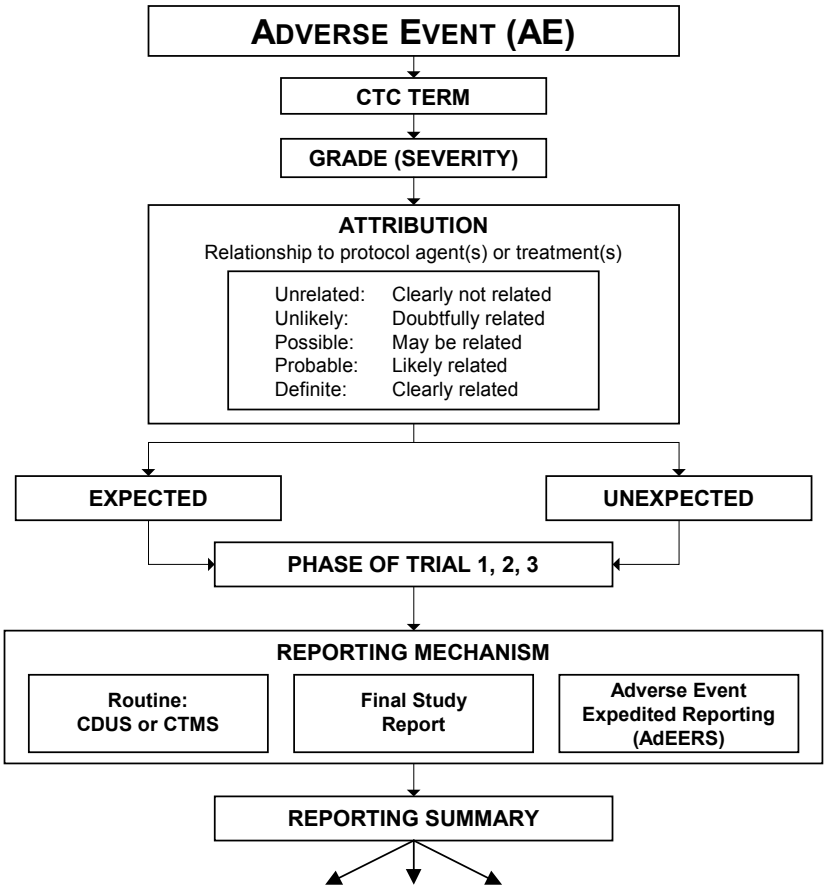
B.3.2.1 By mail: Investigational Drug Branch
P.O. Box 30012
Bethesda, Maryland 20824

B.3.2.2 By fax at 301-402-1584.

Attachment C: THE ADVERSE EVENT REPORTING REQUIREMENT PARADIGM FOR INVESTIGATIONAL AGENTS

The following describes the process for determining if an adverse event is reportable to the NCI.

FIGURE 1: The Adverse Event Reporting Process Flowchart



ATTRIBUTION	GRADE 1		GRADE 2		GRADE 3		GRADE 4		GRADE 5	
	UNEXPECTED	EXPECTED	UNEXPECTED	EXPECTED	UNEXPECTED	EXPECTED	UNEXPECTED	EXPECTED	UNEXPECTED	EXPECTED
UNRELATED	CTMS	CTMS	CTMS	CTMS	CTMS	CTMS	CTMS CDUS AdEERS	CTMS CDUS AdEERS	CTMS CDUS AdEERS	CTMS CDUS AdEERS
UNLIKELY	CTMS	CTMS	CTMS	CTMS	CTMS	CTMS	CTMS CDUS AdEERS	CTMS CDUS AdEERS	CTMS CDUS AdEERS	CTMS CDUS AdEERS
POSSIBLE	CTMS CDUS	CTMS CDUS	CTMS CDUS AdEERS	CTMS CDUS	CTMS CDUS AdEERS	CTMS CDUS	CTMS CDUS AdEERS	CTMS CDUS AdEERS	CTMS CDUS AdEERS	CTMS CDUS AdEERS
PROBABLE	CTMS CDUS	CTMS CDUS	CTMS CDUS AdEERS	CTMS CDUS	CTMS CDUS AdEERS	CTMS CDUS	CTMS CDUS AdEERS	CTMS CDUS AdEERS	CTMS CDUS AdEERS	CTMS CDUS AdEERS
DEFINITE	CTMS CDUS	CTMS CDUS	CTMS CDUS AdEERS	CTMS CDUS	CTMS CDUS AdEERS	CTMS CDUS	CTMS CDUS AdEERS	CTMS CDUS AdEERS	CTMS CDUS AdEERS	CTMS CDUS AdEERS

CDUS – CLINICAL DATA UPDATE SYSTEM for Routine Reporting
CTMS – CLINICAL TRIALS MONITORING SERVICE for Routine Reporting
AdEERS – EXPEDITED REPORTING (This includes hospitalization [or prolongation of existing hospitalization] for any event equivalent to CTC Grade 3, 4, 5 which precipitated hospitalization regardless of requirements for Phase of study, expected or unexpected and attribution.)

Note: For Final Study Reporting:

- **Phase 1 and 2 – According to assigned reporting method (e.g., CDUS or CTMS)**